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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,883	04/18/2005	Michel Christian Morre	BKR-110T	9491

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EXAMINER	
XIE, XIAOZHEN	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,883	MORRE ET AL.	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-114* is/are pending in the application.

4a) Of the above claim(s) *59,60,86-110,112 and 114* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-58,61-85,111 and 113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 November 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20071127*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *seq. alignment*.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The Information Disclosure Statement (IDS) filed 27 November 2007 has been entered. Applicant's amendment of the specification filed 30 November 2007 has been entered. Applicant's amendments of the claims filed 30 November 2007 and 7 December 2007 have been entered.

Election/Restrictions

Upon further review, it has been found that Applicant's argument with respect to the Cosenza et al. reference is persuasive, i.e., the IL-7 conformer characterized in the reference contained three disulfide bridges at different positions. However, the limitations of Group I still lack novelty or inventive step and do not make a contribution over the prior art in view of Namen et al. (U. S. Patent No: 5,328,988) (see below). Since the 1st claimed invention has no special technical feature, it cannot share a special technical feature with the other claimed inventions.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-55 are cancelled. Claims 111-114 have been added. Claims 56-114 are pending. Claims 59, 60, 86-110, 112 and 114 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions. Claims 56-58, 61-85, 111 and 113 are under examination to the extent they read on the elected species: A) the amino acid sequence of SEQ ID NO: 2; B) a hematopoietic cell growth factor selected from SCF, G-CSF and GM-CSF; C) a cytokine selected from IL-2; D) an

antigen derived from the hepatitis virus A, B, C or E; and E) a nucleic acid molecule comprising SEQ ID NO: 1.

Drawings

The objection to the drawings (Figures 9, 12 and 16) for failing to show details as described in the specification (drawings not legible) is withdrawn in response to Applicant's submission of newly scanned drawings.

Claim Objections/Rejections Withdrawn

The objection of claim 66 for a typographical error is withdrawn in response to Applicant's amendment of the claim.

The rejection of claims 56 and 61-85 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in response to Applicant's amendment of the claim to limit the IL-7 is from human or simian.

The rejections of claims 71, 80 and 85 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are withdrawn in response to Applicant's amendment of the claims. These rejections include: claim 80 for reciting the phrase "such as"; and claims 71 and 85 for the recitations of "a pH range comprised between 5 to 7.5" (claim 71), and "the effective amount of the drug substance is comprised between about 3 to 300 μg/kg/day" (claim 85).

The rejection of claims 56-58, 61, 66, 67 and 81-84 under 35 U.S.C. 102(b) as being anticipated by Cosenza et al., is withdrawn in response to Applicant's argument that Cosenza et al. teach an IL-7 conformer with a different disulfide structure.

The rejection of claims 62, 68-80, 85 under 35 U.S.C. 103(a) as being unpatentable over Cosenza et al., in view of Namen et al. (U.S. Patent No: 4,965,195), and further in view of Ho et al. (U.S. Patent No: 5,714,141), is withdrawn in response to Applicant's argument as stated above.

The rejection of claims 63-65 under 35 U.S.C. 103(a) as being unpatentable over Cosenza et al., in view of Goldschneiser et al. (Pub. No.: US 2002/0058791 A1), and further in view of Goeddel et al. (U. S. Patent No.: 5,223,408), is withdrawn in response to Applicant's argument as stated above.

New Grounds of Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 68-85 and 113 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *stimulating B or T lymphocyte development and proliferation in a patient with an immunodeficient disease, a patient undergoing cancer therapy, a patient undergoing grafts, a patient infected with a virus or a parasite, or a patient with low CD4 count,* does not reasonably provide enablement for administering to any patient, including any elderly patient, nor for prophylactic treatment.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The instant claims encompass the use of the pharmaceutical composition for prophylaxis. For example, claims 81-84 recite administration of the pharmaceutical composition to any human patient or any elderly human patient, and for prophylactic treatment or preventing opportunistic infections in immunodeficient patients. Applicant discloses in the specification a pharmaceutical composition comprising a human IL-7 conformer that can enhance immune responses by stimulate B or T lymphocyte development and proliferation, and therefore, can be used for therapeutic treatment in a patient with an immunodeficient disease, a patient undergoing cancer therapy, a patient

undergoing grafts, a patient infected with a virus or a parasite, or a patient with low CD4 count. The specification, however, does not provide sufficient support for prophylactic treatment or treating any patient. Totsuka et al. (J. Immunol., 2007, 178(8):4737-48) teach that IL-7 is essential for the development and the persistence of chronic colitis, and that therapeutic approaches targeting IL-7/IL-7R signaling pathway may be feasible in the treatment of inflammatory bowel diseases (see Abstract). Therefore, excessive IL-7 is not always beneficial to any patient. The specification does not teach what the outcome would be if administered the composition into a patient with any disease or to an elderly individual, and whether prevention can be achieved without adverse effects to the patient. It requires large quantity of experimentation to determine the patient population and treatment outcomes, which is undue.

Since the specification fails to provide any guidance for the prophylactic treatment or to treat a patient with any disease, the skilled artisan would need to pick up one of the diseases and determine how to treat the disease and what outcome to expect. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification.

Due to the large quantity of experimentation necessary to determine whether the claimed pharmaceutical composition can be used for prophylactic treatment or treating any disease, the lack of direction/guidance presented in the specification, the absence of working examples directed to same, the complex nature of the invention, the state of the art which teaches that IL-7 can confer chronic colitis in a subject, and the breadth of

the claim which encompasses prophylaxis and administration to any human patient, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 56-58, 61-63, 66-71, 73-77, 80-85, 111 and 113 are rejected under 35 U.S.C. 102(b) as being anticipated by Namen et al. (U. S. Patent No: 5,328,988, issued on 12 July 1994).

The claims are directed to a composition of matter comprising a recombinant human IL-7 conformer and a pharmaceutical composition thereof, wherein said conformer comprises the following three disulfide bridges: Cys:1-4 (Cys2-Cys92); 2-5 (Cys34-Cys129) and 3-6 (cya47-Cys141), wherein the total amount by weight of said IL-7 conformer in the composition is at least 98% or 99.5% by weight, and wherein said composition is substantially free of IL-7 molecular variants or another conformer or product related impurities (claims 56, 57, 66-68, 111, 113); wherein the IL-7 conformer comprises the amino acid sequence of SEQ ID NO: 2 (claim 58); wherein the IL-7 conformer is glycosylated or non-glycosylated (claims 61, 62); wherein the IL-7 conformer is associated to HGF as a heterodimer (claim 63); wherein the pharmaceutical composition comprising one or more pharmaceutically acceptable

carriers, e.g., sucrose (claim 69), and is contained in an isotonic buffer with pH between 5 to 7.5 (claims 70, 71); wherein the pharmaceutical composition is in a lyophilized form (claim 73), and further comprises a surfactant or a protein (claim 74); wherein the pharmaceutical composition further comprises an immuno-stimulating agent selected from a hematopoietic cell growth factor (e.g., SCF, G-CSF, GM-SCF), a cytokine (e.g., IL-2), and an adjuvant that facilitates the immunogeneicity of an antigen and able to induce a Th1-type immune response (claims 75-77, 80); wherein the pharmaceutical composition is for administration to a human patient for stimulating B or T lymphocyte development and proliferation, to reduce opportunistic infections in immunodeficient patients, and to prolong lymphopoiesis stimulation (claims 81-84); wherein the effective amount of the pharmaceutical composition is between 3-300 μg/kg/day (claim 85).

The '988 patent teaches a substantially homogeneous recombinant human IL-7 polypeptide free of contaminating endogenous materials (col. 13, lines 38-42). The '988 patent teaches that the human IL-7 comprises the amino acid sequence of residues 1-152 of Fig. 5, which is identical to the SEQ ID NO: 2 of the instant invention (Fig. 5). The '988 patent teaches that the human IL-7 can be glycosylated or non-glycosylated (col. 13, lines 42-53). The '988 patent teaches that the human IL-7 polypeptide can include other sequence imparting desired characteristics, e.g., stabilization or simplified purification of expressed recombinant product (col. 10, lines 44-49). The '988 patent teaches a composition comprising the human IL-7 for therapeutic uses, and the composition comprising the purified protein in conjunction with physiologically acceptable carriers, excipients or diluents, such as neutral buffered saline or saline

mixed with conspecific serum albumin (col. 16, lines 17-30). The '988 patent teaches that preferably, the product is formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents (col. 16, lines 30-32). The '988 patent teaches that the composition can be used in conjunction or admixture with other lymphokines, e.g., GM-CSF, IL-2 (col. 16, lines 13-16). The '988 patent teaches addition of adjuvants, e.g., plant lectin concanavalin A (ConA) or phytohemaglutinin (PHA), to augment the response of IL-7 as a T-cell mitogen (col. 31, line 1-57). The '988 patent teaches that the composition is used for stimulating B and/or T lymphocyte development or proliferation or modulating or augmenting immune, lymphopoietic, or hematopoietic response in mammals, including humans (col. 16, lines 4-13). The '988 patent teaches that the dosage is generally 10 ng to 100 μg/kg/day (col. 16, lines 32-38).

While the '988 patent does not expressly teach the disulfide bond positions, this structural feature would reasonably have been considered to be inherent to the human IL-7 molecule since the tertiary structure of a protein is an intrinsic feature resulting from its primary structure. Also, the hu-IL-7 of the '988 patent has exactly the same biological activities as recited in the claims. A compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Case law has established that the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Further, the structural feature of the disulfide bond pattern, i.e., Cys:1-4 (Cys2-Cys92); 2-5 (Cys34-Cys129) and 3-6

(cya47-Cys141), has been taught by Srinivasan et al. (Protein Engineering, 1993, vol. 6, suppl., pp. 107). Thus, the Srinivasan et al. publication constitutes further evidence of the inherency of the disulfide bond pattern of the IL-7 disclosed by '988.

While the '988 patent does not expressly teach the amino acid sequence of human IL-7 comprising the sequence of SEQ ID NO: 2, this structural feature would reasonably have been considered to be inherent to the human IL-7 molecule since the hu-IL-7 of the '988 patent has exactly the same biological activities as recited in the claims. A compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Case law has established that the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Further, the amino acid sequence of human IL-7 has been taught by Namen et al. (U. S. Patent No: 5,705,149, issued on 6 January 1998), which has 100% local similarity to SEQ ID NO: 2 of the instant invention (see sequence alignment, Result 3). Thus, the '149 patent constitutes further evidence of the inherency of the amino acid sequence of the IL-7 disclosed by '988.

While the '988 patent does not expressly teach that the human IL-7 is associated to HGF as a heterodimer, this property would reasonably have been considered to be inherent to the human IL-7 molecule since the hu-IL-7 of the '988 patent has exactly the same biological activities as recited in the claims. A compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Case law

has established that the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Further, Lai et al. (J. Immunol., 2001, 167:3550-3554) teach that IL-7 forms a heterodimer with the free mitogenic β-chain of HGF/SF (pp. 3550, Introduction section). Thus, the Lai et al. reference constitutes further evidence of the inherency of the HGF binding property of the IL-7 disclosed by '988.

Therefore, the '988 patent anticipates the instant claims.

Claims 56-58, 61-63, 66-71, 73-75, 78-85, 111 and 113 are rejected under 35 U.S.C. 102(b) as being anticipated by Ho et al. (U.S. Patent No: 5,714,141, issued on 3 February 1998).

The instant claims are as stated above. The claims are also directed to a pharmaceutical composition wherein it further comprises an antigen, such as Hepatitis A, B, C or E virus (claims 78 and 79).

The '141 patent teaches the use of recombinant human IL-7 in a pharmaceutical composition to improve the potency of a vaccine, e.g., Hepatitis B vaccine (col. 3, lines 63-67; col. 4, line 67 bridging col. 5, line 2). The '141 patent teaches the composition comprising IL-7 and the vaccine (col. 8, lines 12-19). The '141 patent also teaches other limitations recited in the instant claims. For example, the '141 patent teaches that rhuIL-7 is highly purified (col. 9, lines 43-46), can be recombinantly prepared from any source

(glycosylated and non-glycosylated forms) (col. 8, lines 1-5). The '141 patent teaches that the pharmaceutically acceptable carrier includes sugars (sucrose), isotonic agents, and gelatin (a protein), and the pharmaceutical composition is in a lyophilized form (col. 6, lines 43-65). The '141 patent teaches the improvement of the potency of vaccination by the use of an adjuvant I the vaccination protocol (col. 5, lines 36-43). The '141 patent teaches the dose of the compounds from 1 nM to about 5 μM/kg of body weight (col. 7, lines 37-48). The '141 patent teaches that administration of rhuIL-7 increases the precursor and mature B lymphocytes while having some effect on T lymphocytes, and that rhuIL-7 has also been shown to accelerate the recovery of lymphocytes in either cyclophosphamide-treated or sublethally irradiated, immune-suppressed mice (col. 1, lines 28-33). The '141 patent teaches administering the composition to human patients with various diseases or conditions, including HIV infection and cancer (col. 7, lines 49-67; col. 6, lines 36-41).

With respect to the limitations of the disulfide bond positions, the amino acid sequence, and dimerization with HGF of human IL-7, theses are would reasonably have been considered to be inherent to the human IL-7 molecule as set forth above.

Therefore, the '141 patent anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 64 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Namen et al. (U. S. Patent No: 5,328,988), or Ho et al. (U.S. Patent No: 5,714,141), in view of Goeddel et al. (U. S. Patent No.: 5,223,408, issued on 29 June 1993).

The '988 patent or the '141 patent teaches as set forth above. The '988 patent or the '141 patent, however, does not teach that the IL-7 conformer is functionally attached to an Fc portion of IgG1 or a human arum albumin (HAS) (claims 64, 65).

The '408 patent teaches conjugating an IL-7 polypeptide with IgG1-Fc or albumin to increase half-life ((column 6, line 36; column 19, lines 33-43).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the '988 patent or the '141 patent, with those of the '408 patent, to conjugate IL-7 with IgG1-Fc or HAS. One of ordinary skill in the art would have been motivated to combine the teachings, because the '988 patent or the '141 patent teaches the use of rhu-IL-7 for stimulating B and/or T lymphocyte development and proliferation or modulating immune responses in humans, and the '408 patent teaches that conjugating IL-7 with Ig Fc or albumin can increase half-life. Therefore, the combined teachings provide a reasonable expectation of successfully modulating IL-7-mediated immune responses.

Claim 72 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ho et al. (U.S. Patent No: 5,714,141), in view of Morozov et al. (U.S. Patent No: 5,728,680, issued on 17 March 1998).

The '141 patent teaches as set forth above. The '141 patent, however, does not teach that the pharmaceutical carrier contains a sodium citrate or an ammonium acetate buffer (claim 72).

The '680 patent teaches pharmaceutical compositions for treating Hepatitis B virus infection, e.g., Hepatitis B vaccine, that is formulated with excipients, such as sodium citrate (col. 31, line 49 bridging col. 32, line 12).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulating a pharmaceutical composition comprising both IL-7 and Hepatitis B vaccine with sodium citrate as an excipient, since using it instead of the carrier taught by the '141 patent amounts to a simple substitution of one known, equivalent element for another to obtain predictable results. This leads to the reasonably expected success due to ordinary skill and common sense, not innovation. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>).

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph. D.
February 12, 2008

/Elizabeth C. Kemmerer/

Primary Examiner, Art Unit 1646